2016

Is Vitamin D Supplementation Effective at Reducing Idiopathic Musculoskeletal (MSS) Pain?

Darra O. Markland
Philadelphia College of Osteopathic Medicine, darrama@pcom.edu

Is Vitamin D Supplementation Effective at Reducing Idiopathic Musculoskeletal (MSS) Pain?

Darra O. Markland, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 18, 2015

Abstract

Objective: The objective of this selective EBM review is to determine "Is Vitamin D supplementation effective at reducing idiopathic musculoskeletal (MSS) pain?"

Study Design: Review of primary studies published between the years 2012-2014.

Data Sources: One double blind randomized controlled trial (RCT), one semi-crossover RCT, and one before and after observational study. These were found using Cochrane Review and PubMed databases.

Outcomes Measured: Clinical outcomes were measured in these studies utilizing the Visual Analogue Scale for Pain, the 5-point Likert Pain Scale, the Standard Nordic Questionnaires and numerical grading of pain level, and number of pain sites before and after Vitamin D_3 supplementation.

Results: In a RCT by Knutsen et. al (2014), pain scores were improved in the experimental group receiving supplementation with Vitamin D_3 as compared to placebo, but results were not significant. The double-blind, semi-crossover RCT by Schreuder et. al (2012) found significant improvement in nonspecific MSS pain after 6 weeks of Vitamin D_3 supplementation and mixed results after 12 weeks of supplementation. The before and after observational study performed by Le Goaziou et. al (2014) also found significantly decreased pain sensation in participants after Vitamin D_3 supplementation as compared to baseline.

Conclusions: There is conflicting data in regard to the relationship between Vitamin D stores and MSS pain. To determine whether or not Vitamin D_3 supplementation significantly improves idiopathic MSS pain, there needs to be more double-blind randomized controlled trials performed for analysis.

Keywords: Vitamin D, musculoskeletal pain

INTRODUCTION

Pain is the most common complaint that health care providers treat.[1] Chronic pain is characterized as painful symptoms lasting for at least a three month duration.[2] Pain of musculoskeletal origin can be the result of underlying disease processes such as inflammatory or autoimmune conditions, infections, neoplasms, renal deficiency, hyperlipidemia, advanced age, pharmacotherapeutic reactions, or idiopathic in origin.[1] Whether there is a link between Vitamin D deficiency and idiopathic musculoskeletal pain is controversial. This paper evaluates three clinical trials that considered the efficacy of Vitamin D_3 supplementation for improving nonspecific, idiopathic musculoskeletal pain.

More than 20% of outpatient visits are based on musculoskeletal complaints (both chronic and acute), comprising more than 315 million outpatient visits annually.[1] The average healthcare expenditure on chronic pain management in the US is $125 billion, with low back pain alone costing around $86 billion.[2] Vitamin D deficiency, defined as 25(OH)D serum levels less than 20 ng/mL, affects 29% of post-menopausal women and 25% of men over the age of 65 years old in the U.S.[3] Recent interest in the potential sequelae of Vitamin D deficiency, including musculoskeletal pain, has prompted over-the-counter Vitamin D supplementation purchases to rise nearly 10-fold throughout the early 2000's.[4]

It has been proposed that chronic pain is influenced by three key factors: an incurable disease, unresolved neural factors from a previous disease, or psychological conditions such as anxiety or depression.[2,5] However, these explanations do not account for the etiology or pathophysiology of idiopathic musculoskeletal pain. It is known that the sensation of pain itself is due to neuropathic processes originating in the body's nociceptive sensory stimuli.[5] These communicate via the thalamus, brainstem and somatosensory cortex to evoke an emotional

response regulated by both the limbic system and neurotransmitters such as serotonin and norepinephrine.[5] Vitamin D might indirectly have an effect on this pain perception since it enhances bone mineral composition by increasing the body's absorption of calcium and phosphorus.[3] Theoretically, this could have a profound impact on musculoskeletal symptoms as hypocalcemia predisposes individuals to rickets and osteomalacia while hypophosphatemia can induce muscle weakness, bone pain and decreased bone integrity.[3,6] In support of this theory, a higher frequency of musculoskeletal pain has been reported among Vitamin D deficient individuals indigenous to areas with low sunlight exposure.[7] Furthermore, Vitamin D receptors are found in most cells and tissues throughout the body, including muscle cells and immune cells, reinforcing its potential influence on idiopathic musculoskeletal pain.[3]

Since idiopathic musculoskeletal pain has unknown causation, the current standard approach to treatment is multidisciplinary and palliative. This includes NSAIDs and acetaminophen for mild to moderate symptom relief along with heat and cryotherapy.[3] Modalities such as physical therapy and acupuncture can be beneficial as well.[3] Long-acting opioids, such as morphine and oxycodone, are implemented with caution for debilitating pain unresponsive to aforementioned approaches.[2] Because chronic musculoskeletal pain can be a psychosomatic manifestation of an underlying psychiatric disorder, a trial of cognitive behavioral therapy or tricyclic antidepressants can sometimes reveal an undiagnosed mood disorder and provide relief.[2] The pathophysiology of Vitamin D suggests a potentially promising and affordable treatment alternative for joint and muscle pain with a favorable risk-benefit ratio.

OBJECTIVE

The objective of this selective EBM review is to determine "Is Vitamin D supplementation effective at reducing idiopathic musculoskeletal (MSS) pain?"

METHODS

This investigation looks at two double-blind randomized controlled trials, including one semi-crossover study, and one observational before and after study. Each study included both male and female Vitamin D deficient participants with similar demographic parameters amongst experimental and placebo groups in the controlled trials.[7,8,9] Knutsen et. al utilized one experimental group combined of participants receiving 10μg or 25μg of Vitamin D_3 as compared to a control group receiving a visibly matched placebo.[7] The semi-crossover controlled trial by Schreuder et. al gave one experimental group a single 150,000 IU dose at baseline and again at 6 weeks, the second experimental group a 150,000 IU dose of Vitamin D_3 at baseline followed by a visually matched placebo at 6 weeks, and the third group received a placebo at baseline followed by a single 150,000 IU dose of Vitamin D_3 at 6 weeks.[8] Outcomes at 6 weeks and 12 weeks were measured.[8] Participants in the before and after observational study received between 400,000 to 600,000 IU of Vitamin D_3 dependent upon individual baseline serum Vitamin D levels.[9] All studies examined patient oriented outcomes by evaluating changes in MSS pain from baseline in response to improved Vitamin D deficiency.[7,8,9]

This systematic review included searches in the Cochrane Review and PubMed databases. The two randomized controlled trials were published in peer reviewed English journals between the years of 2012 to 2014. Le Goaziou et. al published their work in French the 2014 Edition of the European Journal of General Practice, which was then translated into English. Key words utilized to find these articles were “Vitamin D” and “musculoskeletal pain.” Each study utilized similar inclusion and exclusion criteria with more stringent exclusion parameters in the two controlled trials as demonstrated by Table 1. The inclusion criteria included adults aged 18 to 60 years-old with chronic MSS pain of unknown origin who had been

diagnosed with Vitamin D deficiency. This review attempted to exclude studies with participants who had comorbidities that could interfere with Vitamin D metabolism. The inclusion and exclusion criteria for each study is outlined below (see Table 1).

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Schreuder (2012)	Semi-crossover randomized controlled trial	84	18-60 years old	≥ 1 parent born in a non-Western country. Vitamin D <50 nmol/L. > 3 nonspecific MSS pain episodes of >1 month duration in 2 years, or ongoing for 3 months, without obvious cause	Pregnancy, Rickets, Sarcoidosis or Tuberculosis. Use of statins, cyclosporines or oral steroids. Use of Vitamin D in last 4 mo's. Ca > 2.55 mmol/L. Cr > 150 mmol/L ESR > 30 mm/h.	5 lost to f/u in the first 6 wks. 10 lost to f/u in the second 6 wks.	1 dose of Vitamin D_3 150,000 IU verses placebo. Evaluated at 6 wks and again at 12 wks
Knutsen (2014)	Double-blind randomized controlled trial	251	18-50 years old	Assumed healthy population experiencing MSS pain. Vitamin D <50 nmol/L. Born in or children of parents born in the Middle East, Africa or South Asia.	Same as above except no exclusion of statins or cyclosporines and no lab testing parameters. Plus exclusion of breastfeeding, CA, renal disease, osteoporosis, recent fracture and the use of pain killers, thiazides, epileptics or HRT	36	Vitamin D_3, 10 µg or 25 µg PO qd x 16 weeks
Le Goaziou (2014)	Before and after observational study	69	18-50 years old	Diffuse MSS pain. Vitamin D <50 nmol/L.	Identified causation of MSS pain	20	1 dose of 400-600,000 IU Vitamin D_3. Examined 45-60 days later.

Schreuder et. al outlined parameters to specify chronicity of pain, classified as at least 3 episodes of 1 month duration of pain for 2 years or continuous pain for 3 months, whereas Knutsen et. al and Le Goaziou et. al selected participants who sought consultation from their general practitioner for MSS pain.[7,8,9] Exclusion criteria included in both randomized controlled trials were pregnancy, renal disease, tuberculosis, sarcoidosis or osteoporosis, and use of Vitamin D supplements or medications that interfere with Vitamin D metabolism. Exclusion criteria specific to Schreuder et. al included signs of rickets, ESR > 30 mm/h, serum calcium > 2.55 mmol/L, and serum creatinine > 150 mmol/L.[8] Exclusion criteria specific to the study by Knutsen et. al included use of strong pain medication, breastfeeding or a recent fracture.[7] Le Goaziou et. al did not disclose exclusion criteria for the observational study, however phototype, body mass index, use of body-covering clothes, diet, sun exposure, pain, fatigue, impact of pain on quality of life and health insurance coverage were considered and matched to the best capacity when selecting study participants.[9]

Statistical analysis in all three studies utilized p values to determine the significance of mean changes in pain from baseline. Only Schreuder et. al reported dichotomous data, which allowed for calculation of the control event rate (CER), experimental event rate (EER), relative benefit increase (RBI), and absolute benefit increase (ABI). The numbers needed to treat (NNT) was then determined from the ABI, while numbers needed to harm (NNH) was not applicable due to absence of significant adverse participant outcomes.[8] This study utilized the Pearson X^2 test to determine an association between VAS reports and Likert Scale scores, which allowed for imputation of missing Likert scales for four participants who were lost to follow up.[8] Knutsen et. al reported the odds ratio (OR) and confidence interval (CI) of the study's results and utilized the Generalized Estimating Equation Poisson Regression Model to adjust outcome variables and

account for the likelihood that reported pain levels were influenced by participants' number of pain sites.[7] Le Goaziou et. al utilized a Chi-Square Test for baseline data to determine post-intervention comparison.[9] The evolution of mean pain scores was then determined with mixed model analysis and adjusted for BMI, age and gender.[9]

OUTCOMES MEASURED

All three studies examined the efficacy of Vitamin D_3 supplementation to decrease MSS pain levels in individuals with Vitamin D deficiency. Knutsen et. al examined its effects on pain parameters as demonstrated by changes in reported MSS pain, utilizing the Standard Nordic Questionnaire, after 16 weeks of supplementation.[7] Schreuder et. al had participants record pain results on the following 5-point Likert Scale: Much Less Pain, Less Pain, Equal Pain, More Pain, or Much More Pain. This was measured at 6 weeks and again at 12 weeks into the study.[8] The location and intensity of pain was also measured with VAS questionnaires, scaled from 0-100 (0 translating as "no pain" and 100 translating as "worst imaginable pain), with consideration of four key pain sites (shoulder, low back, arms and legs and joints).[8] Le Goaziou et. al measured a mean pain evaluation score with a questionnaire that specified the location of pain, duration of pain, intensity of pain, and the use of analgesics.[9]

RESULTS

All three of these studies yielded different results about the effects of Vitamin D_3 supplementation on MSS pain. The Likert scale pain scores collected by Schreuder et. al yielded statistically significant decreases in pain levels, with 34.9% improvement in the Vitamin D_3 group of 44 participants compared to 19.5% improvement in the placebo group of 40 participants ($P=0.04$), yielding 7 numbers needed to treat (see Table 2).[8] These values were calculated with imputation for missing data (however, calculations without imputation also yielded statistically

significant improvement).[8] At 12 weeks, the only statistically significant difference in pain relief on Likert Scales was seen between the group of 24 participants that received Vitamin D_3 for both interventions, with a 61.9% improvement rate, verses the arm comprised of 33 participants that received placebo for the first 6 weeks then Vitamin D_3 for the second 6 weeks, with a 12.6% improvement rate (P=0.005). This difference yielded 3 numbers needed to treat (see Table 2).[8] The difference in pain scales between Vitamin D-Vitamin D vs. Vitamin D-Placebo groups as well as the Vitamin D-Placebo and Placebo-Vitamin D groups in this semi-crossover clinical trial yielded no statistically significant results, with p-values > 0.05 in both instances.[8] This data is based on a total of 79 participants during the first 6 week analysis (after losing 5 participants to follow up) and 69 participants in the second analysis at 12 weeks, resulting in an 18% total loss to follow-up in this study.[8]

Table 2: Calculations for treatment from Schreuder et. al[8]

Intervention	Treatment Interval	CER	EER	RBI	ABI	NNT
Vitamin D vs. Placebo	6 weeks	19.5%	34.9%	78.97%	15.4%	7
Vitamin D-Vitamin D vs. Placebo-Vitamin D	12 weeks	12.6%	61.9%	391%	49.3%	3

The observational study by Le Goaziou et. al also found a statistically significant difference between baseline and post-intervention results. Mean pain values at baseline were 5.1 and decreased to 2.8 when measured at follow up after their single dose of Vitamin D_3 intervention (P<0.001).[9] (See Figure 1) The scaling for reported data was not specified. There were initially 69 participants in this study with a 29% loss to follow-up, resulting in a total of 49 participants.[9]

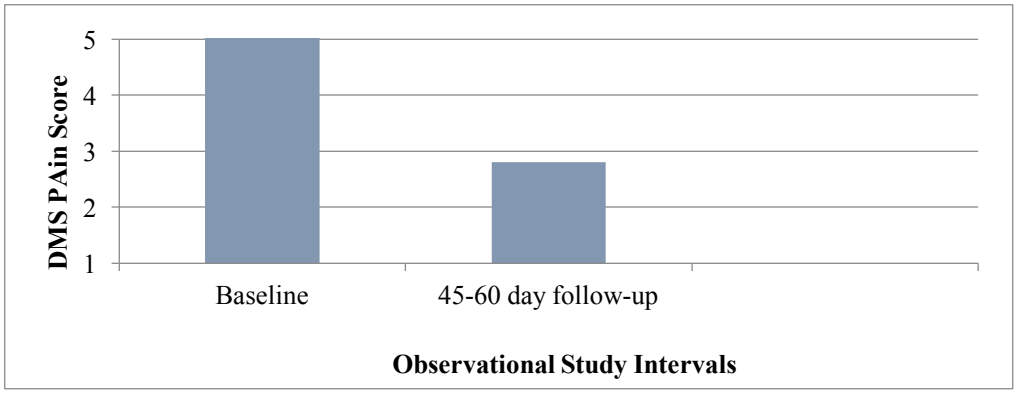

Figure 1: Before and After Study Results for Vitamin D_3 Supplementation by Le Goaziou et. al

The RCT by Knutsen et. al did not demonstrate statistically significant changes in pain level with Vitamin D_3 supplementation. The Vitamin D group reported a 20% decrease in pain, similar to the control group that reported an 18% decrease in pain (P=0.82).[7] The confidence interval (CI) of these reported results was large (0.34-3.96) and the odds ratio (OR) was 1.15 once values were adjusted for age, gender and baseline Vitamin D_3 level, indicating that the intervention was not effective (See Figure 2).[7] The study began with 251 eligible participants, and concluded with 215 participants, resulting in an approximate 15% loss to follow-up.[7] Out of those participants, 180 individuals returned their Vitamin D_3 tablet boxes as requested for compliance analysis.[7] 80% of the cohort had consumed 80% of the allotted tablets while 69% had consumed 90% of the tablets.[7]

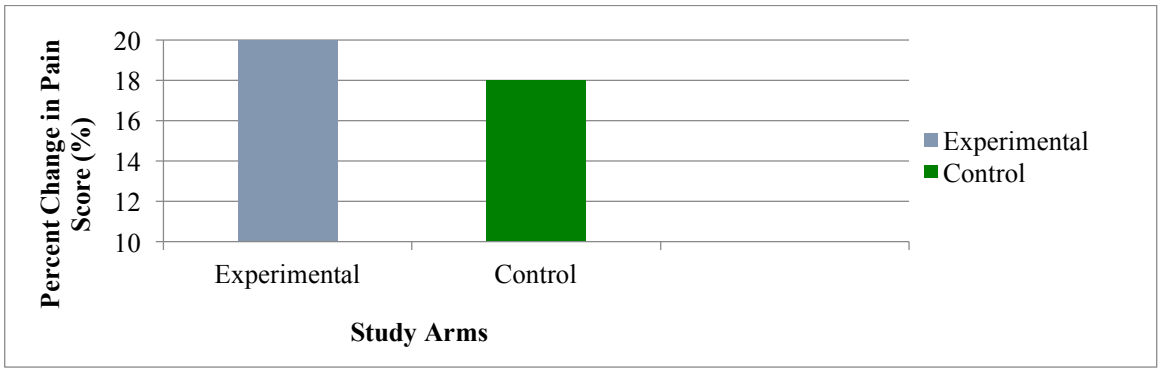

Figure 2: Results for Vitamin D_3 Supplementation by Knutsen et. al

All three studies reported minimal to no adverse effects that were unrelated to the intervention.[7,8,9] Knutsen et. al reported that 21 of their participants experienced new onset of symptoms.[7] However, these were distributed equally amongst placebo and control groups and not attributable experimental supplementation.[7] Vitamin D_3 is a naturally metabolized substance and all participants were deficient in the nutrient. It takes chronic ingestion of more than 40,000-100,000 IU per day to reach Vitamin D_3 toxicity, so this was not of concern.[7,10]

DISCUSSION

Vitamin D_3 has received public attention in recent years for its potential link to chronic conditions such as unexplained depression, MSS pain, cancers, cardiovascular disease and metabolic disorders.[3] The potential efficacy of this nutrient is valuable because patients who seek care for idiopathic MSS pain have few safe and affordable long-term treatment options. Palliative modalities such as physical therapy, massage and acupuncture relief often do not qualify for insurance coverage. Chronic NSAID use can result in gastric bleeding or ulceration, while chronic ASA use can induce hepatotoxicity.[2] Opioids impose risk of dependency and have potent ADR's that interfere with activities of daily living, most notably chronic constipation, cognitive impairment and dependence.[2] Vitamin D_3 is a safe and affordable over-the-counter alternative that is naturally metabolized by the hepatic and renal systems without proven adverse effects when utilized at the recommended daily doses.[3,7-9]

Although two of the included studies demonstrated some improvement in MSS pain with Vitamin D_3 supplementation, limitations in these studies challenge the efficacy of reported results. One key outlier was the inconsistency in regulation of pain relieving medications among participants. Schreuder et. al attempted to standardize this variable by allowing participants to use pain relieving medications and record their usage, which was similar across groups, and

Knutsen et. al measured pain medication uses as an outcome variable.[7,8] However, analgesic effects on pain perception could have a profound impact on reported pain scales. Furthermore, although researchers attempted to match baseline pain levels amongst participants, individualized pain thresholds make it difficult to draw objective conclusions from study results.

There were other limitations that may have affected the outcome of these studies such as the relatively short duration of each trial. For instance, some participants in the study by Knutsen et. al did not surpass the level of Vitamin D deficiency by trial's conclusion.[7] This suggests that a longer duration of supplementation might potentially lead to more pronounced and significant improvements. The RCT by Knutsen et. al also relied on participants to comply with daily doses of Vitamin D_3 supplements, which resulted in altered outcomes from a degree of noncompliance as reported by the study (see Results section). Furthermore, the participant selection criteria for these studies did not account for all of conditions that could affect chronic pain as well as the metabolism of Vitamin D. Of particular concern, these trials did not disclose if screening for psychological conditions was performed. Since mental health conditions can manifest psychosomatically as pain, participants in these studies may have had underlying conditions influencing their pain perception that cannot be treated by vitamin supplementation.[7-9] Additionally, only Schreuder et. al excluded participants who had excess serum concentration of minerals that could influence Vitamin D metabolism and MSS pain. Meanwhile, Knutsen et. al simply excluded a handful of the many conditions that influence these factors and Le Goaziou et. al neglected to outline specific exclusion criteria.[7,8] Without stringent inclusion and exclusion criteria, the efficacy of interventions in these studies is questionable.

Validity was an issue in all three studies. The study by Le Goaziou et. al had the most profound improvement in pain, however it was the least valid study. This research could not

establish a causal effect from the intervention due to the fact that it was an observational study that did not keep participants or researchers blind to the intervention.[9] Furthermore, the study had loss to follow-up rates exceeding 20%.[9] Knutsen et. al did implement a more reliable randomized controlled trial to measure data, however researchers combined the two experimental arms receiving 10μg and 25μg of Vitamin D_3 daily and compared these groups as a whole to the control.[7] It is questionable why the researchers chose this approach, and the grouping of two differently dosed interventions decreases the validity of the results.[7] While Schreuder et. al did find improvement in pain reports via the Likert Scale, there was conflicting data amongst the three study arms.[8] The reason for this is unclear, but the inconsistency decreases the likelihood of reproducible results.

CONCLUSION

Despite its potential appeal, existing data is inconclusive in determining whether or not Vitamin D_3 is an effective means of alleviating idiopathic musculoskeletal pain. Although these studies attempted to account for a number of potential outliers, it is difficult to guarantee validity in studies that rely on patient oriented outcomes such as pain scale due to its subjectivity. In order to control for these factors, future studies designed as double-blind randomized controlled trials need to be taken underway. Future studies should be longer in duration, should have extensive screening protocols for pain-inducing comorbidities, and should implement ongoing extraneous analgesic control. Until more reliable studies are complete, it cannot be confirmed whether supplementation with Vitamin D_3 can improve idiopathic MSS pain in individuals who are Vitamin D deficient.

Works Consulted

1. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. Pain and Its Management. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. *Harrison's Manual of Medicine, 18e.* New York, NY: McGraw Hill; 2013. http://accessmedicine.mhmedical.com/content.aspx?bookid=1140&Sectioni=63497538. Accessed November 19, 2015.

2. Gonzales MJ, Smith GT, Rabow MW, Pantilat SZ. Pain. In: Feldman MD, Christensen JF, Satterfield JM. eds. *Behavioral Medicine: A Guide for Clinical Practice, 4e.* New York, NY: McGraw-Hill; 2014. http://accessmedicine.mhmedical.com/content .aspx? bookid=1116&Sectionid=62690234. Accessed November 19, 2015.

3. Fitzgerald PA. Endocrine Disorders. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *Current Medical Diagnosis & Treatment 2016.* New York, NY: McGraw-Hill; 2016. http://accessmedicine.mhmedical.com/content.aspx?bookid=1585&Sectionid=97195160. Accessed October 11, 2015.

4. The vitamin D dilemma: How much is too much? what you should know about getting tested. Consumer Reports Web site. http://www.consumerreports.org/cro/2012/04/the-vitamin-d dilemma/index.htm. Published May 2011. Updated 2011. Accessed October/09, 2015.

5. Cush JJ. Approach to Articular and Musculoskeletal Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 19e.* New York, NY: McGraw-Hill; 2015.http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectioni=79750978. Accessed November 19, 2015.

6. Wacker M, Holick M. Review: Vitamin D - effects on skeletal and extraskeletal health and need for supplementation. *Nutrients*. 2013;5:111-148. Accessed October 8, 2015
7. Knutsen KV, Madar AA, Brekke M, et al. Effect of vitamin D on musculoskeletal pain and headache: A randomized, double-blind, placebo-controlled trial among adult ethnic minorities in norway. *Pain*. 2014;155(12):2591-2598. doi: 10.1016/j.pain.2014.09.024 [doi].
8. Schreuder F, Bernsen RM, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in non-western immigrants: A randomized controlled trial. *Ann Fam Med*. 2012;10(6):547-555. doi: 10.1370/afm.1402.
9. Le Goaziou MF, Kellou N, Flori M, et al. Vitamin D supplementation for diffuse musculoskeletal pain: Results of a before-and-after study. *Eur J Gen Pract*. 2014;20(1):3-9. doi: 10.3109/13814788.2013.825769 [doi].
10. Potts JT, Jr., Jüppner H. Disorders of the Parathyroid Gland and Calcium Homeostasis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine, 19e.* New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79753597. Accessed December 11, 2015.